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CLINICAL AND EXPERIMENTAL STUDIES ON YANG -DEFICIENCY

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This article reviews recent clinical and experimental investigations of Yang-deficiency. It is evident that pathophysiological changes in Yang-deficient patients are extensive, denoting that Yang-deficiency syndrome in TCM is of material basis.

Extensive research on fundamental principles of traditional Chinese medicine with modern scientific methods has been done in China recently. Syndromes of *Yin* and *Yang* are the most important of the eight categorical syndromes in TCM, and syndromes of *Yin*-deficiency and *Yang*-deficiency, each having peculiar manifestations of prolonged duration, offer many advantages for scientific investigation. This article reviews recent clinical and experimental research on *Yang*-deficiency syndrome and *Yang*-tonifiers.

Criteria of Yang-deficiency Syndrome

It is understood that the criteria for diagnosis of individual syndromes must be unified before fruitful results can be obtained from clinical studies. Controversial results in past *Yang*-deficiency studies have arisen primarily from difference of criteria used. For instance, the former diagnostic criterion of *Yang*-deficiency used in Shanghai First Medical College was based on a combination of major and minor manifestations. Major manifestations included (1) consistant aversion to a cold environment, especially in winter, and (2) edema. Minor manifestations included (1) pallor, (2) loose bowel and increased volume of clear urine, (3) *Qi*-deficiency, (4) impotence, (5) moist plump tongue, and (6) slow deep pulse. Two major and one minor manifestations were essential for the diagnosis of *Yang*-deficiency.[1]

This criterion was revised in 1978, and in the new criterion major manifestations include (1) aversion to a cold environment and cold extremities, (2) puffy face, and (3) pale plump tongue with moist fur. The minor manifestation are (1) frequent urination at night, (2) loose bowel and increased volume of clear urine, and (3) slow weak pulse. According to this criterion, *Yang*-deficiency is diagnosed by the combination of two major and one minor manifestations.[2]

Diagnostic criterion suggested by the Shanghai Second Medical College[3] is somewhat different. Major manifestations are pale plump tongue, moist tongue fur, slow weak pulse, aversion to cold, cold extremities, high tolerance of heat in summer, easy fatigue and weakness and drowsiness. The minor manifestations include shortness of breath, lassitude, spontaneous sweating, pallor, loose bowel and clear increased urine and frequent urination at night.

The diagnostic criterion of *Yang*-deficiency of the Shanghai College of Traditional Chinese Medicine[4] is simillar to that of Shanghai First Medical College proposed in

1964, but diagnosis is established on one major and three minor manifestations. Other medical colleges still have their own diagnostic criteria. These different criteria should be unified through discussion, so that the data of various researchers will be comparable.

The above-mentioned criteria of diagnosis are for patients, but they may also be useful in experimental investigations. For example, "aversiveness to cold" may be changed to "shortened tolerance to cold" (or "lowered rectal temperature" in mouse experiments).

"Yang-deficiency" Animal Models

In medical research, the animal modelling of disease is an established procedure; but animal modelling of syndromes of traditional Chinese medicine is a new problem and there is as yet no accepted animal modelling of classical "*Yang*-deficiency". Administration of cortisone or hydrocortisone to mice is commonly used, the dose being 0.5-1 mg/day. After about one week the animals appear inactive, dispirited, huddled up, bent-bodied, with withered hair, the caudal part prolapsed, and unable to open the eyes or becoming blind. This diseased animal is deficient of vital energy, with "symptoms of cold" as shown in a swimming time test and cold tolerance test. The status of the animal corsponds well to *Yang*-deficiency in many spects.[5]

Other methods of modelling "*Yang*-deficient" animals are administration of methylthiouracil or "cold-property" herbal drugs (coptis root, philodendron bark, rhubarb, or gypsum, etc., in excess), or partial ignition of the adrenal gland in rats. The latter methods are less commonly used, however.

These "*Yang*-deficient" animal models have an obvious shortcoming in that the modelling process is acute, and in most animals the result of acute or subacute drug reactions. Compared to clinical studies, the animals are different from the chronic course of *Yang*-deficiency in man. Besides, clinical *Yang*-deficiency syndrome is always linked with syndromes of the viscera, such as deficiency of *Spleen-yang*, deficiency of *Kidney-yang*, etc. It is probable that the animal model may represent both the deficiency of *Yang* and disease of a certain viscera. The hypertension model in rats caused by partial ignition of the adrenal gland may be relieved by *Yang*-tonifiers, decoction of Radix Aconiti Praeparata附子 and Cortex Cinnamomi 肉桂, so the model may represent the *Yang*-deficiency of the *Kidney*, but not that of other viscera. The "*Yang*-deficiency" model induced by ingestion of Radix et Rhizoma Rhei displays diarrhea and other gastrointestinal symptoms, so the model may represent the *Yang*-deficiency of the *Spleen*, but not that of the *Kidney* or other viscera.

The validity of a "*Yang*-deficiency" model may be further tested by treatment with proven *Yang*-tonifiers. If the symptoms of the model are relieved, the diagnosis is probably correct. If the treatment fails, the diagnosis is questionable. However, due attention must be paid to the biphasic action (adaptogen-like action) of the traditional Chinese drugs. Certain herbs may be effective in contradictory dysfunctions, such as hypofunction and hyperfunction. So the diagnosis of a model as "*Yang*-deficiency" can not be made solely by its being cured with *Yang*-tonifiers.

Success of "*Yang*-deficiency" modelling also depends on the type, body weight, sex and strain of the animals used. The animals used to date are all small ones (rats, mice, etc.) which physiologically differ markedly from human beings. Larger animals or primates, (pigs, monkeys, etc.) would be preferable.

Immunology in Yang-deficiency

Patients with chronic bronchitis of the *Yang*-deficiency type mostly exhibit immunological hypofunction. *Yang*-deficiency patients of other diseases also show hypoimmunity, and cell-mediated immunity is more affected than humoral immunity. When symptoms of deficiency of *Kidney-yang* are corrected by warming the *Kidney* to reinforce *Yang*, the immunological deviations of the patients are also improved.[6]

In *Yang*-deficiency animal experiments the function of cell-mediated immunity is impaired, and the application of *Yang*-tonifiers can promote the formation of antibodies. It has been shown that leucopenia induced by immunosuppressors may be improved by *Yang*-tonifiers such as Fructus Psoraleae 补骨脂 . Experiments also show that such *Yang*-tonifiers as Herba Epimedii 淫羊藿, Cornu Cervi Pantotrichum 鹿茸, Semen Cuscutae 菟丝子 and others accelerate the transformation of lymphocytes. The phagocytosis of macrophagocytes can also be promoted by Herba Epimedii. Cortex Cinnamomi, Rhizoma Curculiginis 仙茅 , Semen Cuscutae and Herba Cynomorii 锁阳 can raise the level of immunoglobulin.[7]

Metabolism and Vegetative Nervous System in Yang-deficiency

Aversion to a cold environment and cold extremities, both closely related to metabolism, are prominent manifestations in *Yang*-deficiency patients. Basal metabolic rate in these patients is low, as are blood pressure and pulse rate. The cold pressor test yields an erratic result, often an initial decrease rather than an increase in the blood pressure, which may then be followed by fluctuation above and below the baseline. These patients also have less perspiration.

These symptoms reflect the dysfunction of the vegetative nervous system and the preponderance of the para-sympathetic nervous function. There are decreased urinary catecholamines in *Yang*-deficiency patients. Chronic bronchitis patients of the *Yang*-deficiency type show lowered serum citric acid and increased serum lactic acid levels. The significance of the change is that microcirculation is impaired and causes chronic anoxia. The aerobic oxidation procedure is suppressed. ATP in red blood cells is also decreased[8], and carbohydrate catabolic rate lowered to 24% below normal.

Lowered oxygen consumption rate has been found in "*Yang*-deficient" animals. The animals also have a low tolerance to cold. Acid and alkaline phosphatase in submandibular gland cells of the animals are decreased, and treatment with *Yang*-tonifiers may raise the levels of these enzymes.[9] Glycogen in the cells of "*Yang*-deficient" animals is increased[10], and most enzymes, such as succinic dehydrogenase, etc., are decreased in amount. These findings and the change in DNA (described below) demonstrate that pathophysiology of *Yang*-deficiency includes dysfunction of carbohydrate, protein and fat metabolism, and *Yang*-tonifiers may restore the metabolism of the organism to normal levels.

It has also been shown that *Yang*-tonifiers have a biphasic effect; that is, they may correct both hypermetabolism and hypometabolism.

Assays of trace elements in the blood of *Yang*-deficient or *Yin*-deficient patients demonstrate that serum copper levels in both types are significantly elevated. Normally serum copper level is 1.12, but is 1.26 in *Yang*-deficient and 1.52 in *Yin*-deficient patients. Ratios of Zn/Cu are decreased in both *Yang*-deficient and *Yin*-deficient patients, more markedly in the latter. Besides, serum bromide level in *Yang*-deficient patients is lowered significantly, from normal value

4.33 to 3.75 in *Yang*-deficiency.[11] The trace elements are important in the action of enzymes and hormones and in changes of cell membranes. The relationship between *Yang*-deficiency and variation in trace elements is worth further study.

The values of galvanic skin reflex (GSR) in *Yang*-deficient patients are very low (9.8) compared to normal control (31.9), a statistically significant difference. The GSR values of *Yin*-deficient patients, however, are much higher (48.0), and the change is not significant statistically as compared with normal subjects. The depressed GSR of *Yang*-deficient patients may be revived by *Yang*-tonifiers. It appears that GSR is closely related to metabolism of the body.

The pathogenesis of hypometabolism of *Yang*-deficient patients is yet unclarified. Blood thyroxine levels estimated in *Yang*-deficient patients, except those with hypothyroidism, are within normal range. Whether the hypometabolism is due to low T_3 syndrome or change in thyroxine-binding globulin is still unknown.

Pathological Findings in Yang-deficiency

Autopsy of patients with *Yang*-deficiency reveals degeneration and atrophy in endocrine glands, such as the pituitary, adrenal gland, testis and ovary.

The description of myocardial infarction in traditional Chinese medicine is *Yang*-deficiency or perishing of *Yang*, in most cases, and some *Yang*-tonifiers, such as two new flavones of Fructus Psoraleae (psoraline A and psoraline B), may significantly increase the coronary circulation in the isolated heart of guinea pig. It may be assumed that *Yang* in heart may correlate with coronary circulation. Prepared Radix Aconiti Praeparata, an important *Yang*-tonic, has strong cardiovascular actions, such as hypotensive action, but hypertensive action when used in shock, and contractility depressing action. Its pharmacologic properties have been widely studied by scientists in China and abroad.

Yang-deficient patients are sometimes anemic, and *Yang*-tonifiers are beneficial to the erythropoietic system and the nervous system.

Studies on "*Yang*-deficient" models reveals that the thymus, spleen, and endocrine glands are markedly atrophied. Histological examination of the liver shows hypertrophic hepatic cells with decreased intracellular nucleic acid. Decreased Kupffer's cells and marked decrease of lymphocytes are shown in the spleen.[10] Cells and capillaries in the tongue tip of these models are also decreased, but may, however, increase to normal after *Yang*-tonifier treatment.[9] Under electromicroscopy, nuclei of liver cells show pyknosis, increased heterochromatin accumulation under internal nucleus membrane. There are small spaces between internal nucleus membrane and heterochromatin. Mitochondria are swollen. Cristae are dissolved and have disappeared, but all these may recover after *Yang*-tonifier treatment.[14]

Hypothalamus-pituitary-adrenal Axis in Yang-deficiency

Clinically, most patients with *Yang*-deficient type diseases show decreased urinary 17-OHCS. Further investigations reveal an intact adrenal cortex, and metopirone test and diurnal rhythm of blood corticoids demonstrate sufficient reserve of pituitary ACTH, suggesting dysfunction of hypothalamus as the cause of lowered 17-OHCS. This dysfunction is reversible and with disappearance of symptoms of *Yang*-deficiency, urinary 17-OHCS may return to normal.

Some *Yang*-deficient patients show very low 17-OHCS in urine, but blood cortisol levels are within normal range. In other cases, lowered urinary 17-OHCS may be accom-

panied by both normal urinary free cortisol and blood cortisol.[15] The pathogenesis of these is yet unclarified, but might be due to abnormal degradation.

Some clinical studies demonstrate that *Yang*-tonifiers have beneficial effects both on *Yang*-deficient Sheehan's syndrome and Addison's disease. It is assumed that the site of action of *Yang*-tonifiers may be located in the hypothalamus or the higher central nervous system, and that the effect on the adrenal cortex is only secondary.

During the total solar eclipse, the hypofunction of the pituitary-adrenal cortex of *Yang*-deficient patients was even more marked. 17-OHCS in urine was even lower and salivary sodium excretion increased. The urine catecholamine excretion in patients with "non-*Yin*-deficient excessive fire" was increased during the eclipse. This phenomenon may be a reflection of "relevant adaptation of the human body to its the natural environment".[16]

Gonadal Function in Yang-deficiency

Many *Yang*-deficient patients, particularly those with deficiency of the *Kidney-yang*, have an associated dysfunction of the gonad, with impotence or other symptoms of gonadal hypofunction. Some warm *Yang*-tonifiers, such as Cornu Cervi Pantotrichum, are beneficial to hypogonadism.

Urine 17-OHCS may not be lowered in acute myocardial infarction of the *Yang*-deficient type, but plasma estradiol and testosterone levels are slightly lowered. The ratio of E_2/T is 0.009 ± 0.002, a value slightly higher than normal.[17]

The Relationship between Yang-deficiency and Cyclic Nucleotides

The theory of *Yin-Yang* covers every aspect of body functions, and it is rational to investigate *Yin-Yang* in man from the point of molecular biology.

In 1973 Goldberg proposed the dualism or *Yin-Yang* hypothesis of biological control, describing a form of regulation through dual, opposing actions of the two cyclic nucleotides — cAMP and cGMP.

Subsequently Shanghai Second Medical College studied cyclic nucleotide levels in patients with deficiency syndrome and demonstrated that there is no definite change in the absolute values of blood cAMP and cGMP in *Yang*-deficient patients.[3] In some *Yang*-deficient patients, however, cAMP is diminished but cGMP is increased, and in some other cases both are raised. But the variation in ratio of cAMP/cGMP is regular (around 5 in normal persons), and lowers to about 2.5 in *Yang*-deficient patients of either type. Generally, cAMP is dominant in *Yin*-deficiency, and cGMP in *Yang*-deficiency, giving rise to the significant difference in cAMP/cGMP ratio between the two types. After *Yang*-tonifier treatment, the ratio of cAMP/cGMP in *Yang*-deficiency may be corrected. Studies by Shanghai College of Traditional Chinese Medicine,[4] show that blood or urine cAMP in *Yang*-deficiency does not respond to excessive stress as *Yin*-deficiency does. This may explain at least partly the difference of cAMP between *Yang*-deficiency and *Yin*-deficiency.

Yang-deficiency and DNA

The general condition of the body is closely related to protein synthesis in the cells. It has been found in clinical studies that the protein synthesis of patients with deficiency syndromes is diminished.[10]

We have used hydrocortisone to produce a "*Yang*-deficiency" model in mice, and have demonstrated a significantly lowered DNA renewal rate in the mice models (only 50% compared with the control group).[18] This conforms to the results obtained by other investigators and the histochemical studies by Shanghai College of Traditional Chinese

Medicine.[10] The DNA renewal rate in normal animals receiving *Yang*-tonifiers is the same as the control group, with no increase demonstrated. But in the "*Yang*-deficiency" group, *Yang*-tonifiers may increase the renewal rate of DNA to approximately normal level. However, *Yang*-tonifiers cannot lower the mortality of "*Yang*-deficient" animals. The explanation may be that though the drugs may correct the DNA synthesis of the animals, the impairment of such basic functions can not be remedied in such a short period. That *Yang*-tonifiers can improve the lowered renewal rate of DNA but not the normal rate tallies with the TCM concept of "readjusting *Yin* and *Yang* till restoration of relative equilibrium is reached."

Recently we have studied the action of four *Yang*-tonifiers — Radix Aconiti Praeparata, Cortex Cinnamomi, Herba Cistanchis 肉苁蓉 and Herba Epimedii — on the DNA synthesis of "*Yang*-deficient" animals. In traditional Chinese medicine these drugs are all classified as *Yang*-tonifiers, but with different characteristics. The former two have pungent and hot properties and the latter two are warm sweet tonics nourishing the *Liver* and the *Kidney*. It is very interesting to note that the latter two drugs have a distinct effect on DNA synthesis, whereas the former two are ineffective.[19]

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